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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,315	01/16/2004	Gregory T. Bleck	GALA 08484	9065

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EXAMINER	
POPA, ILEANA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,315	BLECK ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-18,20-26,28 and 30-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12-18, 20-26, 28, and 30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Wee33333DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/04/2007 has been entered.

Claims 11, 13, 19, 27, 29, and 42 have been cancelled.

Claims 1-10, 12-18, 20-26, 28, and 30-41 are pending and under examination.

2. All objections/rejections pertaining to claim 27 are moot because Applicant cancelled the claim in the response filed on 09/04/2007.

3. The rejection of claims 1-10, 12, 14-18, 20-26, 28, and 30-41 under 35 U.S.C. 112, first paragraph, as introducing new matter is withdrawn in response to Applicant's arguments. It is noted that the application claims priority to the U.S. Patent No. 6,852,510, which discloses a genome comprising 20 integrating vectors.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as

to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-10, 18, 20-26, 28, 30-34, 39, and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-20, 22, 28-37, 42-46 of copending Application No. 10/397079. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a method for transducing host cells by providing at least one host cell comprising a genome and a plurality of retroviral vectors encoding a gene of interest, contacting the host cell at a multiplicity of infection from about 10 to 1000, repeating the above steps a plurality of time, clonally selecting the host cell

expressing the gene of interest, and purifying the protein of interest (claims 1-10, 28, and 30). The retroviral vector comprises MoMLV elements (claim 18), the gene of interest is operably linked to an exogenous promoter (claim 20) and to a nucleic acid encoding a secretion signal sequence (claim 21), and the vector encodes at least two proteins, such as immunoglobulin heavy and light chains, arranged in a polycistronic sequence (claims 22-24 and 39). Clonally selected cells express various amounts of protein of interest (claims 32-34), and the host cell comprises from 20 to about 100 integrated retroviral vectors (claim 41). The host cell can be a Chiese hamster ovary cell (claim 26). The specification defines that the retroviral vector lacks a selectable marker and that host cell is stable over extended periods of time, i.e., the integrated exogenous gene of interest is stable in the absence of selection (p. 1, paragraphs 0007 and 0009).

The application claims recite (i) a method for transfecting host cells by providing a plurality of host cell comprising a genome and a plurality of integrating vectors, wherein the integrating vectors lack a gene encoding for a selectable marker, contacting the host cell with the plurality of integrating vectors to generate transfected cells comprising at least 20-100 integrated copies of the integrating vectors, and clonally selecting the transduced cell (claim 18), the integrated exogenous gene is stable in the absence of selection (claim 19), the multiplicity of infection is greater than 10 (claim 20), and the integrating vector is a retroviral vector (claim 28), the host cell synthesizes various amounts of protein (claims 29 and 30, and (ii) a method of producing a protein of interest by providing a host cell comprising a genome, wherein the genome

comprises from 20 to about 100 copies of at least one integrating vector encoding for an exogenous gene encoding for a protein of interest operably linked to a promoter, wherein the integrating vector lacks a gene encoding for a selection marker, and wherein, and wherein the cells are cultured to produce the protein of interest (claims 32 and 42). The method further comprises clonally selecting host cells (claims 35-37). The integrating vector is a retroviral vector (claim 43), the host cell synthesizes various amounts of protein of interest (claims 44-46). The specification discloses that the host cells are serially transfected with the integrating vectors encoding the same gene until the desired level of copies per genome and protein expression is achieved (p. 17, paragraph 0175), that the retroviral vector is a lentiviral vector comprising MoMLV elements (p. 1, paragraph 0009, p. 13, paragraph 0137), that the gene of interest is operably linked to an exogenous promoter (paragraph 0012), that the genes of interest can be arranged in a polycistronic sequence (p. 7, paragraph 0082), that the genes of interest can be immunoglobulins (p. 11, paragraph 0118, p. 18, paragraph 0183), and that the host cells can be Chinese hamster ovary cells (p. 12, paragraph 0133). Thus, the application claims 18-20, 22, 28-37, 42-46 anticipate the instant claims 1-10, 18, 20-26, 28, 30-34, 39, and 41. Since the claims of the Application No. 10/397079 embrace all limitations of the instant claims, the application claims and the instant claims are obvious variants of one another.

Applicant submits that a terminal disclaimer will be filed upon resolution of the remaining rejection. The rejection is maintained until a terminal disclaimer is filed or the claims are amended to obviate the rejection.

6. Claims 1-10, 12, 14-18, 20-26, 28, 30-34, and 39-41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-12 and 14-22 of U.S. Patent No. 6,852,510. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to a method for transducing host cells by providing at least one host cell comprising a genome and a plurality of retroviral vectors encoding a gene of interest, contacting the host cell at a multiplicity of infection from about 10 to 1000, repeating the above steps a plurality of time, clonally selecting the host cell expressing the gene of interest, and purifying the protein of interest (claims 1-10, 28, and 30). The retroviral vector is pseudotyped (claims 12, 14-17) and comprises MoMLV elements (claim 18), the gene of interest is operably linked to an exogenous promoter (claim 20) and to a nucleic acid encoding a secretion signal sequence (claim 21), and the vector encodes at least two proteins, such as immunoglobulin heavy and light chains, arranged in a polycistronic sequence (claims 22-24 and 39). Clonally selected cells express various amounts of protein of interest (claims 32-34), and the host cell comprises from 20 to about 100 integrated retroviral vectors (claim 41). The host cell can be a Chiese hamster ovary cell (claim 26) and the host cell can be transduced with at least two different vectors encoding different genes of interest (claim 40). The

specification defines that the host cell is stable over extended periods of time, i.e., the integrated exogenous gene of interest is stable in the absence of selection and therefore the host cell does not produce infectious retroviral particles (p. 1, paragraphs 0007 and 0009).

The patent claims recite (i) a method for transducing host cells comprising providing a host cell comprising a genome and a plurality of retroviral vectors, contacting the host cell with the plurality of retroviral vectors at a multiplicity of infection greater than 100 under conditions that at least two retroviral vectors integrate into the host cell genome, wherein the retroviral vector comprises at least one exogenous gene encoding for a secreted protein, operably linked to a promoter, wherein the host cell does not produce infectious retroviral particles (claims 9-12, and 14). The retroviral vector is pseudotyped (claim 15; see also Example 2), the host cell can be a Chinese hamster ovary cell (claim 16), the host cell can be transduced with at least two different vectors each encoding different genes of interest (claim 17), and (ii) a method of producing a protein of interest by providing a clonally selected host cell, such as Chinese hamster ovary cell, wherein the host cell genome comprises from about 20 to about 50 integrated copies of retroviral vector encoding for a secreted protein, and culturing the host cell such that the rate of protein production is from 10 pg to 50 pg per cell per day (claims 18-22). Thus, the patent claims 9-12 and 14-22 anticipate the instant claims 1-10, 12, 14-18, 20-26, 28, 30-34, and 39-41. Since the claims of the U.S. Patent No. 6,852,510 embrace all limitations of the instant claims, the application claims and the instant claims are obvious variants of one another.

Applicant submits that a terminal disclaimer will be filed upon resolution of the remaining rejection. The rejection is maintained until a terminal disclaimer is filed or the claims are amended to obviate the rejection.

7. Claims 1-10, 12, 14-18, 20-26, 28, 30-34, and 39-41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 110-124 of copending Application No. 11/018,895. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a method for transducing host cells by providing at least one host cell comprising a genome and a plurality of retroviral vectors encoding a gene of interest, contacting the host cell at a multiplicity of infection from about 10 to 1000, repeating the above steps a plurality of time, clonally selecting the host cell expressing the gene of interest, and purifying the protein of interest (claims 1-10, 28, and 30). The retroviral vector is pseudotyped (claims 12, 14-17) and comprises MoMLV elements (claim 18), the gene of interest is operably linked to an exogenous promoter (claim 20) and to a nucleic acid encoding a secretion signal sequence (claim 21), and the vector encodes at least two proteins, such as immunoglobulin heavy and light chains, arranged in a polycistronic sequence (claims 22-24 and 39). Clonally selected

cells express various amounts of protein of interest (claims 32-34), and the host cell comprises from 20 to about 100 integrated retroviral vectors (claim 41). The host cell can be a Chinese hamster ovary cell (claim 26) and the host cell can be transduced with at least two different vectors encoding different genes of interest (claim 40). The specification defines that the host cell is stable over extended periods of time, i.e., the integrated exogenous gene of interest is stable in the absence of selection and therefore the host cell does not produce infectious retroviral particles (p. 1, paragraphs 0007 and 0009).

The application claims are drawn to (i) a method for transducing host cells comprising providing a host cell comprising a genome and a plurality of retroviral vectors, contacting the host cell with the plurality of retroviral vectors such that at least 20 retroviral vectors integrate into the host cell genome, wherein the retroviral vector comprises at least one exogenous gene encoding for a secreted protein, operably linked to a promoter, wherein the host cell does not produce infectious retroviral particles (claims 110-113). The retroviral vector comprises at least two exogenous genes (claim 115). The retroviral vector is pseudotyped (claim 116), the host cell can be a Chinese hamster ovary cell (claim 117), the host cell can be transduced with at least two different vectors each encoding different genes of interest (claim 118), and (ii) a method of producing a protein of interest by providing a clonally selected host cell, such as Chinese hamster ovary cell, wherein the genome of the host cell comprises a plurality of integrating retroviral vector encoding for a secreted protein, and culturing the host cell such that the rate of protein production is from 10 to about 100 pg per cell per

day (claims 119-124). The specification defines that the at least two genes can be arranged in a polycistronic sequence and that they can be the immunoglobulin heavy and light chains (p. 1, paragraph 0009). Thus, application claims 110-124 anticipate the instant claims 1-10, 12, 14-18, 20-26, 28, 30-34, and 39-41. Since the claims of the U.S. Application No. 11/018,895 embrace all limitations of the instant claims, the application claims and the instant claims are obvious variants of one another.

Applicant submits that a terminal disclaimer will be filed upon resolution of the remaining rejection. The rejection is maintained until a terminal disclaimer is filed or the claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. (1996, cited in form PTO-892 on 05/18/2005), in view of both Felts et al. (1999, cited in form PTO-892 on 05/18/2005) and Inaba et al. (1998, cited in form PTO-1449 on 05/18/2005).

Mathor et al. teach a method of transducing keratinocyte stem cells by contacting them with a retroviral vector containing MoMLV LTRs, wherein the vector encodes for

human interleukin 6 (hIL-6), and wherein the keratinocyte stem cells integrate multiple proviral copies in their genome (claims 1-10, 18, and 41) (Abstract, p. 10371, column 2, second paragraph, Material and Methods) and wherein the transduced keratinocytes secrete hIL-6 at a rate of approximately 800 ng per 10^6 per day during their lifetime (p. 10372, columns 1 and 2, p. 10373, column 2). Since hIL-6 is secreted, the retroviral vector must necessarily comprise a segment encoding a secretion signal sequence operably linked to the gene encoding for hIL-6, as recited in claims 20 and 21). The transduced cells are grown as mass cultures or are cloned by limiting dilution (claims 1, 30, and 31) (p. 1372, column 1). Mathor et al. teach clonal analysis by Southern blot and by radioimmunoassay, wherein the radioimmunoassay is performed on isolated hIL-6 (claims 1, 28, and 30) (p. 10372, columns 1 and 2, p. 10374, p. 13075, column 1 and Fig.4, p. 10636, column 1). Mathor et al. teach 11 clones with 1 to 15 proviral integrations (p. 10373, Table 1). Mathor et al. also teach that the retroviral vector is produced from packaging cell lines transfected with an envelope plasmid and a vector plasmid, wherein the packaging cell line expresses gag and pol proteins (claims 12 and 14) (p. 10371, column 2 bridging p. 10372).

Mathor et al. do not specifically teach a genome comprising from 20 to about 100 integrated vectors (claims 1 and 41), a multiplicity of infection from about 10 to 1000 (claim 1), or clones expressing 10, or 50 pg of protein per cell per day (claims 32-34). Felts et al. teach that the advantage of using retroviral vectors is the ease of controlling the copy number of integrated provirus by varying the multiplicity of infection (MOI) (p. 74). It would have been obvious to one of skill in the art, at the time the invention was

made, to use different MOIs to achieve the claimed ranges of integration events, with a reasonable expectation of success. The motivation to do so is provided by Mathor et al., who teach the importance of specifying the level of transgene expression for gene therapy (Abstract, p. 10371, column 1 bridging column 2, p. 10376, column 1, last paragraph). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that integration events can be easily controlled by manipulating the MOI. With respect to the limitation recited in claims 32-34, these are not innovative over the prior art; one of skill in the art would have had known to obtain the desired amounts of synthesized proteins by controlling the number of integration events.

Mathor et al. do not teach serially transducing the cells (claims 2-10). Inaba et al. teach a method of transducing cells by contacting the cells with viral supernatant 4-6 times over a 10-14 day period, wherein serially transducing the cells results in an increased transduction efficiency (p. 32, column 2, first paragraph, Fig.1, p. 34, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. by using serial transduction, with a reasonable expectation of success. The motivation to do so is provided by Inaba et al., who teach that serial transduction results in higher transduction rates. Given these teachings, one of skill in the art would have found it obvious to repeat the infection protocol as many times as necessary to achieve the desired level of protein production. One of skill in the art would have been expected to have a reasonable expectation of

success in using such a method because the art teaches that serial transduction can be successfully used to increase transduction efficiency.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that the Examiner's reasoning with respect to the teachings of Mathor et al., Felts et al., and Inaba et al. are inconsistent with the understanding of one of skill in the art when considering the art as a whole. Applicant draws attention to the declaration of Dr. Gregory Bleck, one of the inventors of the instant application and person of ordinary skill in the art. In his declaration, Dr. Bleck asserts that the art teaches away from producing cell lines with high MOIs, such as an MOI of 100, and from producing a cell line with more that 20 integrated vectors per cell, since Coffin et al. teach that insertional mutagenesis is often a safety concern; this issue was raised because proviral insertion can cause inactivation of tumor suppressor genes and the activation of onogenes. Applicant argues that Arai teaches that proviral integration with very high copy numbers seems to cause cell death, and therefore, upon reading Arai, one of skill in the art would be discouraged from using the claimed multiplicity of infection and copy insert number to obtain a cell line for the production of a secreted protein. Applicant argues that one of skill in the art understands that conditions that would result in more than 15 integration fall within the category of high copy numbers and thus would be discouraged from exceeding the conditions taught by Arai. Applicant asserts that one of skill in the art would not have known to use routine experimentation

to determine what MOI results in 20 to 100 integrations. Applicant also argues that a person of skill in the art by reading Coffin et al. would be discouraged from using transduction conditions that lead to high numbers of integrations and insertional mutagenesis, and that such concerns would apply both *in vivo* and *in vitro*. Applicant asserts that that the fact that the teachings of Coffin et al. are directed to the *in vivo* use does not mitigate that insertional mutagenesis is a problem that should be addressed and avoided. Applicant conscludes that, since transduction of cells with concentrated retroviral vectors causes insertional mutagenesis and cell death, one of skill in the art would not have been motivated to use such conditions. Since the claimed invention was not predictable based on the prior art as a whole, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

While Applicant's arguments regarding Taruscio et al. are found persuasive, the arguments regarding Arai et al. and Coffin et al. are not. Arai et al. teach that the number of proviral integrations (and therefore, protein production) can be increased by increasing MOI (p. 112, column 1, Fig. 3) and that 15 integrations can be obtained with a MOI of 30. Although they teach that proviral integration with a very high copy number seems to cause cell death, Arai et al. do teach that not cells are dying and therefore, one of skill in the art would have known to use routine experimentation to clone the viable cells that contain a very high number of integration events and produce cell lines that synthesize high amounts of recombinant protein. Therefore, the art does not teach

away from the claim invention. In response to Applicant's argument that one of skill in the art would not be motivated to attained the claimed ranges, it is noted that the art teaches the number of integrations per cell as being a result-affecting variable and therefore, one of skill in the art would be motivated to use a range of integrations (obtained by varying MOIs) to obtain optimum results. One of skill in the art would use only routine experimentation to optimize the results, and by doing this one of skill in the art would have necessarily obtained integrations within the broad range of 20 to 100. Regarding the argument that Coffin teaches that insertional mutagenesis by retroviral vectors is a safety concern, it is noted that Coffin refers to the *in vivo* use of retroviral vectors in animals and humans. Applicant's assertion of safety concern is not an issue in the instant case, because the claims encompass a host cell *in vitro* and the combined teachings of Mathor et al. and Felts et al. are drawn to the *in vitro* production of recombinant proteins. Applicant's argument that the teachings of high numbers of integrations and insertional mutagenesis would apply both *in vivo* and *in vitro* is not found persuasive because Coffin et al. refers to gene therapy in humans where malignant transformation can endanger the patient life, which cannot be compared to a cell in culture, wherein malignant transformation does not endanger anybody's life and does not impede the cell from producing the protein of interest (see also below).

Applicant argues that, by reading Arai et al. and Coffin et al., one of skill in the art would be discouraged from using transduction conditions that lead to high numbers of integrations or that one of skill in the art would not have known to use routine experimentation to determine what MOI results in 20 to 100 integrations. However,

these arguments are not supported by evidence. On the contrary, the art provides plenty example of obtaining cells comprising more than 20 integrated copies in their genome, wherein increasing integration events are obtained by increasing MOI, demonstrating that varying MOI to obtain more than 20 integration events is routine in the art. Thus, the art clearly demonstrates that one of skill in the art would not have been discouraged by the teachings of Arai et al. and Coffin et al. For example, Kustikova et al. (Blood, 2003, 102: 39343937) teach obtaining clones comprising 21 and 31 proviral copies in the genome, wherein increased integration events correlates with increased transgene expression (p. 3935, Table 1, p. 3936, Fig 1B, p. 3937, column 1, second paragraph). Similarly, Zielske et al. (Molecular Therapy, 2004, 9: 923-931) teach obtaining clones with integration events from 3 to 135 (p. 926, column 1, first full pargagraph, column 2, first full paragraph, p. 928, column 2 and Table 1). Therefore, the art demonstrates that one of skill in the art was clearly not discouraged to use routine *in vitro* techniques to obtain viable clones of cells comprising more than 15 proviral copies integrated in their genome. This is consistent with the teachings of Arai et al. that, even if very high proviral integration rates seems to cause cell death, not all cells are dying; one of skill in the art would have known to use routine experimentation to clone the viable cells that contain high numbers of integration events and produce cell lines that synthesize high amounts of recombinant protein. Therefore, the art does not teach away from the claimed invention and the rejection is maintained.

10. Claims 1-10, 12, 14-18, 20, 21, 26, 28, 30-34, and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of Burns et al. (1993, cited in form PTO-1449 on 05/18/2005).

Mathor et al. taken with Felts et al. and Inaba et al. do not teach 293-GP cells (claim 15), VSV-G protein (claims 16 and 17), or baby hamster kidney (BHK) cells (claim 26). Burns et al. teach producing retroviral vectors pseudotyped with VSV-G, wherein the vectors are produced in 293-G cells and wherein the pseudotyped retroviral vectors are able to mediate stable gene transfer in cells that cannot be infected by the wild type retroviral vectors, such as BHK cells (claim 26) (Abstract, p. 8033, columns 1 and 2, p. 8035, column 1, second paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. taken with Felts et al. and Inaba et al. by using the pseudotyped retrovirus of Burns et al., with a reasonable expectation of success. The motivation to do so is provided by Burns et al., who teach that such a virus has an expanded host range. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Burns et al. do not cure the deficiencies noted for the combination of Mathor et al., Felts et al., and Inaba. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

11. Claims 1-10, 12, 14, 18, 20, 21, 26, 28, 30-38, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of Schroder et al. (1997, cited in form PTO-892 on 05/18/2005).

Mathor et al. taken with Felts et al. and Inaba et al. do not teach DHFR and culturing the transduced cells in the presence of methotrexate (claims 35-38), nor do they teach Chinese hamster ovary (CHO) cells (claim 26). Schroder et al. teach the amplification of hATIII expression in CHO cells via DHFR-mediated gene amplification in the presence of methotrexate (Abstract, Introduction, Table I). It would have been obvious to one of skill in the art, at the time the invention was made, to include an amplifiable marker, such as DHFR, into the vector of Mathor et al., Felts et al., and Inaba et al. for increase protein production and to use the modified vectorfor the transduction of CHO cells, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schroder et al. teach that increase synthesis of recombinant proteins in animal cells is commonly achieved by using gene amplification. One of skill in the art would have been motivated to use CHO cells because they are known to be an excellent model cell line for the production of high levels of proteins of interest. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Schroder et al. do not cure the deficiencies noted for the combination of Mathor et al., Felts et al., and Inaba. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

12. Claims 1-10, 12, 14, 18, 20-24, 26, 28, 30-34, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of both Primus et al. (1997, cited in form PTO-892 on 05/18/2005) and Kolb et al. (Hybridoma, 1997, 16: 421-426, Abstract).

Mathor et al. taken with Felts et al. and Inaba et al. do not teach at least two different vectors encoding different genes of interest (claim 40). Primus et al. teach a method of expressing a monoclonal IgG2a antibody into a tumor cell, wherein the tumor cell is transduced with two different vectors, one encoding the heavy and the other encoding the light chain (claim 40), and wherein the transduced tumor cell produces self-reactive antibodies (Abstract, p. 3355, column 1, p. 3356, column 1, first full paragraph, p. 3360, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Mathor et al., Felts et al., and Inaba et al. to express antibodies into a cancer cell, as taught by Primus et al., with a reasonable expectation of success. The motivation to do so is provided by Primus et al., who teach that antibody gene transfer into autologous tumor cells offer a new and alternative application in the use of antibodies for the immune therapy of cancer. One of skill in the art would have been expected to have a reasonable expectation of

success in making such a composition because the art teaches that such a composition can be successfully obtained.

Mathor et al. taken with Felts et al. and Inaba et al. do not teach at least two genes of interest arranged in a polycistronic sequence, wherein the genes of interest are the immunoglobulin heavy and light chains (claims 22-24 and 39). Kolb et al. teach concurrent synthesis of both heavy and light chains of the monoclonal antibody A1 by using a bicistronic expression cassette comprising an internal ribosomal entry site (IRES) (Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al., Felts et al., and Inaba et al. by using the expression cassette of Kolb et al. for the production of monoclonal antibodies of interest, with a reasonable expectation of success. The motivation to do so is provided by Kolb et al., who teach that their method allows for the rapid isolation of cell clones expressing high levels of recombinant antibody. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that such a composition can be successfully obtained.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that neither Primus et al. nor Kolb et al. cure the deficiencies noted for the combination of Mathor et al., Felts et al., and Inaba. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

13. Claims 1-10, 12, 14, 18, 20, 21, 25, 28, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of Naldini et al. (1996, cited in form PTO-892 on 05/18/2005).

Mathor et al. taken with Felts et al. and Inaba et al. do not teach a lentiviral vector (claim 25). Naldini et al. teach lentiviral vector for the stable transduction of non-dividing cells (Abstract, p. 263, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al., Felts et al., and Inaba et al. by using the lentiviral vector of Naldini et al., with a reasonable expectation of success. The motivation to do so is provided by Naldini et al., who teach that their vector can be used for the transduction of non-proliferating cells such as hepatocytes, myofibers, hematopietic stem cells, and neurons. One of skill in the art would have been expected to have a reasonable expectation of success in using such a composition because the art teaches that such a composition can be successfully used.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Naldini et al. do not cure the deficiencies noted for the combination of Mathor et al., Felts et al., and Inaba. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kustikova et al. (Blood, 2003, 102: 39343937) and Zielske et al. (Molecular Therapy, 2004, 9: 923-931) were only cited to demonstrate that, as opposed to Applicant's assertion, one of skill in the art has not been discouraged by the prior art to achieve the instant invention.

15. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD